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Tumor immune profiling based neoadjuvant immunotherapy for locally advanced melanoma

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Past

Over the past decade, immunotherapy and checkpoint blockade have revolutionized the treatment of metastatic melanoma. The demonstrated benefit of adjuvant immunotherapy for locally advanced melanoma encouraged the development of clinical trials to assess the role of neoadjuvant immunotherapy in this patient population (1). Two prospective trials have supported the feasibility of neoadjuvant checkpoint blockade for resectable Stage III melanoma (2,3). Both studies reported high rates of objective response to combination therapy with anti-PD-1 and CTLA-4 inhibitors, but a substantial proportion of these patients experienced significant immune-related adverse events (irAEs) that limited the tolerability and duration of their therapy. These studies also reported low response rates with single agent PD-1 blockade (in unselected patients). This study examined the efficacy of neoadjuvant immunotherapy and whether treatment stratification guided by immune profiling can enhance treatment results and avoid unnecessary toxicity.

Present

Our group has previously demonstrated that the percentage of T cells within the tumor microenvironment showing exhaustion markers can predict response to anti-PD-1 monotherapy in the metastatic setting (4), and that tumors with low fraction of exhausted T cells may still respond to combination CTLA-4/PD-1 blockade (5). Immune profiling can therefore be used to stratify therapy groups; patients with favorable profiles can receive anti-PD-1 monotherapy and avoid the toxicities of anti-CTLA-4 agents while patients unlikely to respond to monotherapy receive combination immunotherapy. This study applied this immune profiling based stratification to 17 patients with resectable stage III or oligometastatic stage IV melanoma (6). Ten patients received anti-PD-1 monotherapy and seven received anti-CTLA-4/PD-1 combination therapy. Sixteen patients (94%) achieved either a complete or partial response, and eight of the 11 patients who underwent subsequent surgical resection attained a complete pathologic response. Only three (17.6%) patients experienced clinically severe (grade 3 or 4) irAEs.

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Future

In alignment with other studies of neoadjuvant immunotherapy in locally advanced melanoma, this study demonstrated a high rate of objective response, relapse free survival, and overall survival. Of note, five patients declined surgery after achieving a complete radiographic response, and all remain disease free at a median follow-up of 27.6 months. In contrast to previous neoadjuvant studies which reported high rates of irAEs, neoadjuvant immunotherapy was well tolerated in our study due to stratification of treatment regimens with immune profiling. These outcomes warrant further investigation of the role of neoadjuvant immunotherapy in melanoma, and specifically the use of biomarkers to guide and optimize treatment regimens to enhance response while minimizing toxicity.

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